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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,397	02/16/2001	Altaf A. Lal	6395-57049	4907

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EXAMINER	
FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	15

DATE MAILED: 02/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,397	LAL ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *7-9,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-6 and 10 in Paper No. 14 filed on January 14, 2002 is acknowledged. Groups II-V, claims 7-9 and 11-12 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. The traversal is on the grounds that Groups I and II form a single general inventive concept. Claim 1 of Group I is the main invention in this application and lacks novelty, therefore the other claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.

Restriction is required under 35 U.S.C. 121 and 372.

The MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term "distinct" is defined to mean that two or more subjects as disclosed are related, for example as product and method of use, etc., but are capable of separate manufacture, use or sale as claimed, and are patentable over each (see MPEP 802.01). In the instant situation, the inventions of Groups I-II are drawn to distinct inventions which are separate products and methods capable of separate manufacture, use or sale as described in the previous Office Action.

The literature search, particularly relevant in this art, is not co-extensive, because for example, Groups I, III and IV are drawn to different products. Group I, claims 1-6 and 10 are drawn to a recombinant protein comprising peptides from two or more stages in a life cycle of *Plasmodium falciparum*, wherein each peptide comprises an antigenic epitope. Group II, claims 7-8 are drawn to an isolated nucleic acid molecule encoding the protein of claim 1. Clearly different searches and issues are involved in the examination of each Group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Objections

2. Claim 10 is drawn to a non-elected invention. Applicant should amend the claim so that is drawn to an elected invention. There is also insufficient antecedent basis for the "composition" limitation in the claim. No other claims under consideration are drawn to a "protein composition".

Claim Rejections - 35 USC § 112

3. Claims 1-6 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID Nos. 2-25, does not reasonably provide enablement for fragments, combination of fragments and conservative substitutions thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a recombinant protein comprising peptides from two or more stages in a life cycle of *Plasmodium falciparum* wherein each peptide comprises an antigenic epitope.

The specification states "that SEQ ID NO:2 is the recombinant protein that is encoded by the gene shown in SEQ ID NO. 1. The specification states" that the "recombinant protein of SEQ ID NO: 2 can be used as a multivalent, multistage vaccine for *Plasmodium falciparum*" (page 3). The specification discloses antigenic fragments used in making the coding sequences used in the construction of the gene are shown in Table 1 (page 16). The specification continues by describing the construction of the recombinant protein by using genetic expression systems and the production of antigenic peptides (pages 8-11).

It is well known in the art that major obstacles to develop an effective Malaria vaccine include the developmental regulation of antigen expression during parasite replication, nonresponsiveness of individuals to particular parasite antigens or epitopes and variability of antigens among different parasite isolates. It is well known that subunit vaccines based on single malarial antigens may fail to protect an individual because of any one of the above mentioned factors. One means of overcoming barriers in regard to formulating an effective Malaria vaccine is to include multiple antigens from different stages of the parasite life cycle. Despite multicomponent strategies the problem of overcoming nonresponsiveness to vaccine components derived from a single life cycle stage remains a difficult one (Tine et al, 1996). This is illustrated in studies using the SPf66 multicomponent *P. falciparum* blood stage vaccine in which 26

to 45 % of inoculated individuals do not seroconvert (Noya et al, 1994 and Valero et al, 1993). Antigenic polymorphism in the parasite reduces the effectiveness of the host immune response. A single amino acid change with in a T-cell epitope is often sufficient to prevent recognition, either by immune escape or altered peptide ligand antagonism of the T cell receptor (Gilbert et al, 1997). Clearly a great amount of experimentation would be necessary in order to obtain an epitope that can retain antigenic activity.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other antigens having claimed functional feature of capability of generating protective responses, 3) the nature of the invention involved the complex and incompletely understood area of protective immune response in regard to antigenic epitopes against *Plasmodium falciparum*, 4) the state of the prior art shows lack of correlates to immunity against *Plasmodium falciparum,* 5) the relative skill in the art is commonly recognized as quite

high (post-doctoral level) and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

The claims of the instant application are not only drawn to a recombinant protein comprising peptides from two or more stages in a life cycle of *Plasmodium falciparum* wherein each peptide comprises an antigenic epitope but also encompasses fragments of the protein of less than about 50 amino acids (page 8). There is no guidance provided as to which "less than about 50 amino acids" would be effective as antigenic fragments.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of prediction protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

The applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with in the scope of the claims broadly including any additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left to those unskilled in the art is unnecessarily and improperly, extensive and undue. See Amgen Inc v. Chugai Pharmaceutical Co Ltd. 927 F 2d 120, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1-26-1-27 and Exparte Forman 230, 230 U.S.P.Q. 546(BD =. App & Int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would be undue experimentation to make or use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 5-6 and 10 are rejected under 35 U.S.C. 102(b) as anticipated by Gilbert et al, *(Nature Biotechnology, Volume 15, November 1997, p. 1280-1284).*

Claims 1-3, 5-6 and 10 are drawn to a recombinant protein comprising peptides from two or more stages in a life cycle of *Plasmodium falciparum* wherein each peptide comprises an antigenic epitope.

Gilbert et al teach recombinant Ty virus-like particles (Ty-VLPs) carrying a string of up to 15 defined cytotoxic T lymphocyte (CTL) epitopes from *Plasmodium* species (see the Abstract). Gilbert et al teach that it is possible to identify epitopes in conserved regions of several *P. falciparum* antigens to formulate a vaccine that may enable the immune system of the host to mount an effective immune response against most or all strains of *P. falciparum* (page 1280). Gilbert et al teach antigenic epitopes that have been used to create a candidate vaccine for *Plasmodium falciparum* malaria and suggest that there are several lines of evidence supporting a protective role for CTL against the liver-stage parasite in the immunity to malaria (page 1280). Gilbert et al further teach antigenic epitopes that comprise a heparin binding motif and epitopes that could impair the ability of sporozoites to invade hepatocytes (page 1282). Gilbert et al teach liver stage epitopes ls6 and ls8 (page 1281, Table 1) that have same amino acid sequences as SEQ ID Nos. 9 and 10, respectively of the claimed invention. Gilbert et al teach B cell epitopes from circumsporozoite (CS) protein (page 1281, Table 1) that have the same amino acid sequence as SEQ ID No: 4 of the claimed invention. The recombinant protein comprising antigenic epitopes of Gilbert, et al appears to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

5. Claims 1-3, 5-6 and 10 are rejected under 35 U.S.C. 102(a) as anticipated by Shi et al, *(Proc. Natl. Acad. Sci, USA, February 1999).*

Claims 1-3, 5-6 and 10 are drawn to a recombinant protein comprising peptides from two or more stages in a life cycle of *Plasmodium falciparum* wherein each peptide comprises an antigenic epitope.

Shi et al teach epitopes derived from 9 T cell stage-specific *Plasmodium falciparum* antigens corresponding to the sporozoite, liver, erythrocytic, asexual and sexual stages. Shi et al teach that a high effective malaria vaccine would require a combination of key antigens and or epitopes from different stages of the life cycle and that induction of both humoral and cellular immunity is required for optimal efficacy (see page 1615). Shi et al teach a merozoite surface protein antigen MSP-2B (page 1616, Table 1) that has the same amino acid sequence as SEQ ID No: 14 of the claimed invention. Shi et al also teach liver stage epitopes LSA-1-CTL (page 1616, Table 1) that have the same amino acid sequences as SEQ ID Nos: 9 and 10 of the claimed

invention. The recombinant protein comprising antigenic epitopes of Shi, et al appear to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shi et al or Gilbert et al . . . in view of Schmitt et al *(Molecular Biology Reports Volume 18, 1993, p.223-230).*

Claim 4 is drawn to the protein of claim 1, further comprising a signal peptide polyhistidine and a T-cell helper epitope.

Shi et al teach antigenic epitopes that correspond to the liver and merozoite life stages of the *Plasmodium falciparum.*

Gilbert teach antigen epitopes that correspond to the liver and sporozoite stages of the *Plasmodium falciparum.*

Shi et al nor Gilbert et al teach the use of a histidine tag.

Schmitt et al teach affinity purification of histidine-tagged proteins (see the Title). Schmitt et al teach that the expression of recombinant proteins is a standard technique in molecular biology and a wide variety of prokaryotic as well as eukaryotic expression systems are currently in use. Schmitt et al teach that a limiting step is often that the purification of the expressed recombinant protein that yield low expression levels are employed (see the Abstract). Schmitt et al teach that short amino acid sequences can be fused to the recombinant protein as a tag (page 223). Schmitt et al teach that a stretch of 6 histidine residues (His-tag) linked to the N- or C-terminal part of a recombinant protein is sufficient to allow a high expression of purified protein (page 229).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the histidine-tag as taught by Schmitt et al to the recombinant protein of Shi et al or Gilbert et al because Schmitt et al teach that a stretch of 6 histidine residues (His-tag) linked to the N- or C-terminal part of a recombinant protein is sufficient to allow purification of the recombinant protein (page 229). It would have been expected barring evidence to the contrary, that the addition of a His-tag to recombinant proteins would allow for high expression of purified protein. The addition of the His-tag is well within the level of skill in the art.

Pertinent Prior Art

7. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(Szarfman et al, Parasite Immunol. 1988, 10:339-351 and Patarroyo et al, Nature, Vol. 328, August 1987).*

Status of Claims

8. No claims are allowed.

Conclusion

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
February 5, 2002

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